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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/869,122	06/25/2001	Shohei Tanaka	Q64929	2326

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EXAMINER
HUI, SAN MING R

ART UNIT	PAPER NUMBER
1617	9

DATE MAILED: 03/27/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/869,122	Applicant(s) TANAKA ET AL.	
	Examiner San-ming Hui	Art Unit 1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 December 2001* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *7 and 9-13* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7 and 9-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The formal drawings filed August 17, 2001 are acknowledged.

The English translation of the International Search Report filed August 17, 2001 is acknowledged.

The cancellation of claims 1-6 and 8 in amendment filed December 17, 2001 is acknowledged.

The outstanding warning of claims 1 and 3; and 2 and 4 for substantial duplicity is withdrawn in view of the cancellation of the claims.

The outstanding rejection of claims 1 and 3 under 35 USC 112, first paragraph is withdrawn in view of the cancellations of the claims.

The outstanding rejection of claims 1, 3, and 8 under 35 USC 112, second paragraph is withdrawn in view of the cancellations of the claims.

The outstanding rejection of claims 1-6 under 35 USC 102 is withdrawn in view of the cancellation of the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 7, 9-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Isomura et al. (US Patent 4,990,503 from the Information Disclosure Statement

received September 20, 2001) in view of Shipman et al. (Leukemia and Lymphoma 1998;32(1-2):129-138 from the Information Disclosure Statement received September 20, 2001), for the essentially the same reasons as stated in the previous office action mailed September 28, 2001.

Isomura et al. teaches the heterocyclic bisphosphonic acid compounds, useful as bone resorption inhibitors, including 1-hydroxy-2-(imidazo[1,2a]pyridin-3-yl)ethane-1,1-bisphosphonic acid can be blended with other pharmaceutically acceptable carrier to form medical composition suitable for oral administration (See particularly Col. 7, line 7-19; col. 9, example 5). Isomura et al. also teaches that 1-hydroxy-2-(imidazo[1,2a]pyridin-3-yl)ethane-1,1-bisphosphonic acid possess a strong bone resorption inhibition activities which can be used in diseases such as metastatic osteocarcinoma (See col. 6, line 4-66, particularly Table 1). Isomura et al. also teaches the oral dosage of 1-hydroxy-2-(imidazo[1,2a]pyridin-3-yl)ethane-1,1-bisphosphonic acid to be useful in inhibiting bone resorption to be 0.1 to 10mg daily (See col. 7, line 7-19).

Isomura et al. does not expressly teach 1-hydroxy-2-(imidazo[1,2a]pyridin-3-yl)ethane-1,1-bisphosphonic acid is useful in a method of treating bone lesion associated with multiple myeloma and multiple myeloma itself. Isomura et al. does not expressly teach the effective dosage of 1-hydroxy-2-(imidazo[1,2a]pyridin-3-yl)ethane-1,1-bisphosphonic acid to be 1 to 20 mg or 3 to 10 mg.

Shipman et al. teaches that bisphosphonates have anti-resorptive activities on bone as well as direct anti-tumor activities (See particularly the abstract). Shipman et

al. also teaches that bisphosphonates can induce apoptosis in human myeloma cell lines (See page 133, col. 2 – page 135, col. 1). Shipman et al. also teaches that potent bisphosphonate, such as clodronate and pamidronate are useful in treating multiple myeloma (See particularly page 131, table 1; page 135, col. 2, conclusion).

It would have been obvious to one skill in the art when the invention was made to employ 1-hydroxy-2-(imidazo[1,2a]pyridin-3-yl)ethane-1,1-bisphosphonic acid, in the dosage herein, a method of treating bone lesions associated with multiple myeloma and multiple myeloma itself.

One of ordinary skill in the art would have motivated to employ 1-hydroxy-2-(imidazo[1,2a]pyridin-3-yl)ethane-1,1-bisphosphonic acid, in the dosage herein, in a method of treating bone lesions associated with multiple myeloma and multiple myeloma itself because it is known that certain potent bisphosphonates are useful in treating multiple myeloma. Therefore, employing any potent bisphosphonates including 1-hydroxy-2-(imidazo[1,2a]pyridin-3-yl)ethane-1,1-bisphosphonic acid would be reasonably expected to be useful in a method of treating bone lesions associated with multiple myeloma and inducing apoptosis in multiple myeloma cells, treating multiple myeloma thereby. Furthermore, the optimization of result effect parameters (dosage range) is obvious as being within the skill of the artisan, absent evidence to the contrary.

It is applicant's burden to demonstrate unexpected results over the prior art. See MPEP 716.02, also 716.02 (a) - (g). Furthermore, the unexpected results should be demonstrated with evidence that the differences in results are in fact unexpected and unobvious and of both statistical and practical significance. *Ex parte Gelles*, 22 USPQ2d

1318, 1319 (Bd. Pat. App. & Inter. 1992). Moreover, evidence as to any unexpected benefits must be "clear and convincing" *In re Lohr*, 137 USPQ 548 (CCPA 1963), and be of a scope reasonably commensurate with the scope of the subject matter claimed, *In re Linder*, 173 USPQ 356 (CCPA 1972). In the instant case, Examples 1-5 in the specification page 16-23 have been considered but are not found persuasive as to the nonobviousness of the claimed invention. In Example 1 in the specification page 16-17, the results of the studies are not conclusive because the dosage used for pamidronate is relatively lower than that of the cited prior art. In Shipman et al., the dose of pamidronate that is effective against multiple myeloma is 90mg; however, the dosage of pamidronate in Example 1 is only 0.1mg/kg, i.e., for an average adult who weighs 70kg, the dosage would be only 7mg. For Examples 2, 3, and 4 in specification page 17-20, there is no comparative data presented for the evaluation of the presence of the unexpected results. For Example 5 in the specification page 21, the data merely demonstrates the fact that both pamidronate and the active compound herein are both effective in inhibiting bone resorption for the first two weeks. Since the claims herein do not recite limitations that are limited to the dosage regimen, administering the drugs for more than two weeks, the results of Example 5, as shown in Figure 3 in the specification, in this much, are seen to be expected results over the cited prior art. No clear and convincing unexpected results are seen over the cited prior art.

Response to Arguments

Applicant's remarks filed December 17, 2001 regarding the cited prior art not teaching the active compound herein being useful in suppressing bone resorption and ameliorating multiple myeloma have been considered but are not found persuasive because the cited prior art clearly teaches that bisphosphonates not only are useful to inhibit bone resorption, but also can induce apoptosis in multiple myeloma cells. Therefore, employing any bisphosphonates including 1-hydroxy-2-(imidazo[1,2a]pyridin-3-yl)ethane-1,1-bisphosphonic acid would have been reasonably expected to be useful in treating bone lesions accompanying multiple myeloma and multiple myeloma itself.

Please note that the claims are drawn to method of treating bone lesions and method of treating multiple myeloma by administering 1-hydroxy-2-(imidazo[1,2a]pyridin-3-yl)ethane-1,1-bisphosphonic acid. Based on the cited prior art, one of ordinary skill in the art would have expected the administration of 1-hydroxy-2-(imidazo[1,2a]pyridin-3-yl)ethane-1,1-bisphosphonic acid to multiple myeloma patients to be useful to treat multiple myeloma and/or bone lesions associated with multiple myeloma.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to San-ming Hui whose telephone number is (703) 305-1002. The examiner can normally be reached on Mon 9:00 to 1:00, Tu - Fri from 9:00 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Minna Moezie, J.D., can be reached on (703) 308-4612. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4556 for regular communications and (703) 308-4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

San-ming Hui
March 24, 2002

MINNA MOEZIE, J.D.
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600